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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,008	09/22/2003	Claude Michel Wischik	088736-0104	5847

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EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
12/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Supplemental Notice of Allowability	Application No. 10/665,008	Applicant(s) WISCHIK ET AL.	
	Examiner Jagadishwar R. Samala	Art Unit 1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Examiner's amendment requested on 09/12/2007*.

2. ☒ The allowed claim(s) is/are *175-179,201-208 and 210*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: *UK 0106953.3*.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date attached
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

MICHAEL G. MARTLEY
SUPERVISORY PATENT EXAMINER

SUPPLEMENTAL

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Richard C. Peet on 09/12/2007

2. The application has been amended as follows:

This listing of claims will replace all prior versions, and listings, of claims in the application.

175. (Currently Amended). A method for determining the Braak stage of neurofibrillary degeneration associated with a tauopathy in a subject believed to suffer from the disease, which method comprises the steps of:

(i) introducing into the subject a ligand that labels aggregated paired helical filament (PHF) tau protein, wherein the ligand is capable of crossing the blood brain barrier, and

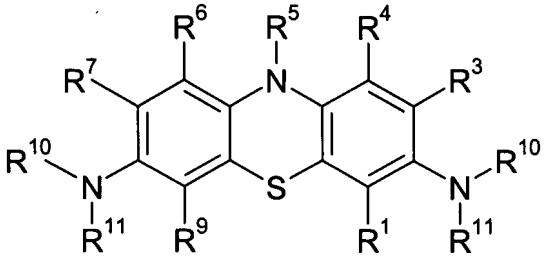
wherein the ligand is conjugated, chelated, or otherwise associated, with a detectable chemical group,

(ii) determining the presence and\or amount of ligand bound to extracellular aggregated PHF tau in the medial temporal lobe of the brain of the subject, and

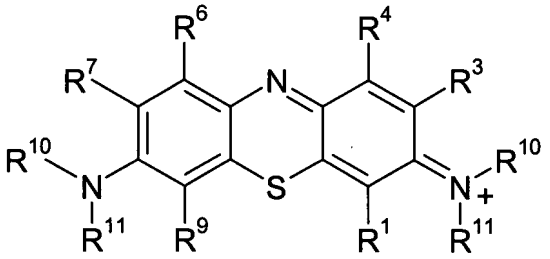
(iii) correlating the result of the determination made in (ii) with the extent of neurofibrillary degeneration in the subject **to determine the Braak stage**,

wherein the method is used for detection of early Braak stages before appearance of clinical symptoms, pre-mortem diagnosis and discrimination of advanced Braak staging**, and**

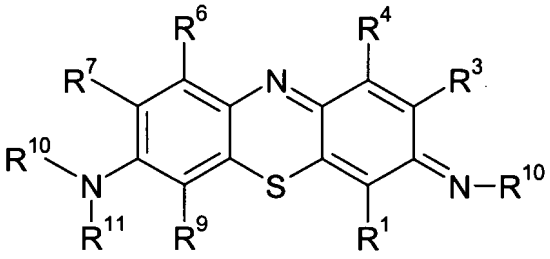
wherein the ligand is a compound of one of the following formulae:



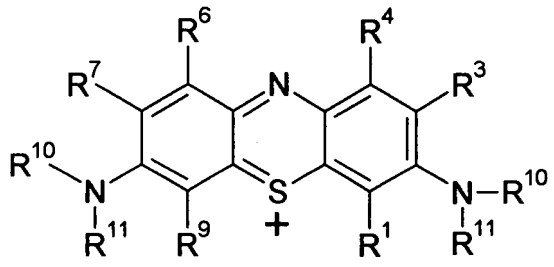
(I)



(II)



(III)



(IV)

wherein:

each of R_1, R_3, R_4, R_6, R_7 and R_9 is independently hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

R_5 is independently hydrogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

R_{10} and R_{11} are independently selected from hydrogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

or a pharmaceutically acceptable salt thereof.

176. (Previously Presented). A method as claimed in claim 175 for use in the diagnosis or prognosis of a tauopathy in a subject believed to suffer from said disease.

177. (Previously Presented). A method as claimed in claim 176 wherein the tauopathy is Alzheimer Disease (AD).

178. (Previously Presented). A method as claimed in claim 175 wherein the extent of neurofibrillary degeneration is related to the Braak neuropathological staging of the progression of AD.

179. (Previously Presented). A method as claimed in claim 175 wherein the ligand is labelled for SPECT and is not absorbed intracellularly or the ligand is labelled for positron emission tomography (PET).

20l. (Currently Amended). A method as claimed in claim ~~200~~ **175** wherein the ligand is an acid addition salt formed between the compound and an acid which is an inorganic acid or an organic acid.

202. (Previously Presented). A method as claimed in claim 201 wherein the ligand is Tolonium Chloride, Thionine, Azure A, Azure B, 1,9-Dimethyl-Methylene Blue or Methylene Blue.

203. (Currently Amended). A method as claimed in claim ~~200~~ **175** wherein the ligand comprises a positron-emitting carbon.

204. (Previously Presented). A method as claimed in claim 175 which further comprises the step of determining the presence and\or amount of a ligand bound to intracellular aggregated tau in a neocortical structure of the brain of the subject.

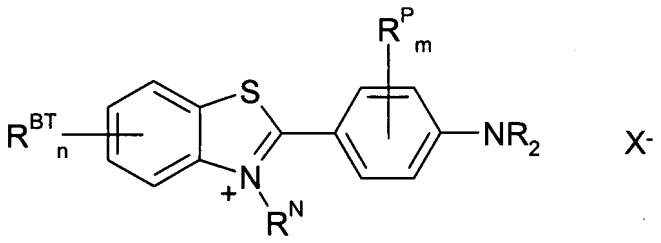
205. (Previously Presented). A method as claimed in claim 204 wherein the ligand used to bind to extracellular aggregated PHF tau in the medial temporal lobe and the ligand used to bind to intracellular aggregated PHF tau in the neocortical structure of the brain are labelled distinctively.

206. (Previously Presented). A method as claimed in claim 175 further comprising the step of introducing into the subject a blocking ligand which labels competing non-

aggregated tau binding sites present in the medial temporal lobe and in a neocortical structure of the brain.

207. (Previously Presented). A method as claimed in claim 206 wherein the blocking ligand is selected from the group consisting of:

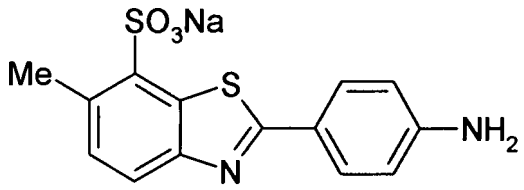
[18F]FDDNP; and a benzothiazole of the formula:



wherein:
n is an integer from 0 to 4; each R^{BT} is independently a blocking ligand benzothiazole substituent which is independently C_{1-4} alkyl, $-SO_3H$, or $-SO_3M^3$, wherein M^3 is a cation, m is an integer from 0 to 4; each R^P is independently a phenyl substituent; each R is independently -H or an amino substituent; and, either: R^N and X^- are both absent and the associated (tertiary) nitrogen atom is neutral; or: R^N is a benzothiazolino substituent and the associated (quaternary) nitrogen atom bears a positive charge, and X^- is a counter ion.

208. (Previously Presented). A method as claimed in claim 207 wherein the blocking ligand is thioflavin-T.

210. (Previously Presented). A method as claimed in claim 207 wherein the blocking ligand is a benzothiazole of the formula:



Cancel claims 1-174, 180-200 and 209.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in United Kingdom on 03/20/2001. It is noted, however, that applicant has not filed a certified copy of the 0106953.3 application as required by 35 U.S.C. 119(b). Applicant is requested to submit a certified copy of United Kingdom 01016953.3 prior to the time of paying issue fee.

Reasons for allowance

4. The following is an examiner's statement of reasons for allowance: Closet prior art found is Peter Friedhoff et al. (Biochemistry 1998, 37, 10223-10230). Peter Friedhoff teaches a method of using the thioflavin S or T derivatives, in the diagnosis, which can be used to stain amyloid-like deposits and neurofibrillary tangles in postmortem brains. The method can be used to quantify the formation of paired helical filaments from tau protein, but fails to teach the claimed invention (i.e., a method for determining the Braak neuropathological staging of Alzheimer disease progression). A thorough search of the prior art did not bring forth a method for determining the Braak stage of neurofibrillary degeneration associated Alzheimer disease.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jagadishwar R. Samala whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jagadishwar R Samala
Examiner
Art Unit 1618

sjr

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER